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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,744	06/02/2000	John Joseph Harrington	9584-0017-999	7865

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EXAMINER

SAIDHA, TEKCHAND

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/586744

Applicant(s)

Harrington et al.

Examiner

T. Saidha

Group Art Unit

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—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 6/19/01 (Paper # No)
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-73 is/are pending in the application.
- Of the above claim(s) _____ is/are withdrawn from consideration.
- ☒ Claim(s) 1-6 is/are allowed.
- ☒ Claim(s) 7-73 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

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1. Applicants' amendment filed 6.19.01 (Paper No. 11) and compliance with sequence rules (Paper No. 27) is acknowledged.
2. Claims 1-73 are under consideration in this examination.
3. A second Third Party Protest under C.F.R. 1.291 for this reissue application has been filed (1.9.2002, Paper No. 18) has been considered and is made of record.
4. A response to the above cited protest filed 6.25.02 (Paper No. 26) has also been considered and is also made of record.
5. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).
6. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

7. ***Surrendering the Original Patent***

This reissue application was filed without the required offer to surrender the original patent or, if the original is lost or inaccessible, an affidavit or declaration to that effect. The original patent, or an affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

There is no record of regarding an offer to surrender the original patent, filed along with response to the Notice of File Missing Parts, as claimed by the Applicants.

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8. *New Matter*

Claims 7-73 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought.

Applicant argue that 'It is well settled that amendments that replace subject matter incorporated into an application by reference with the **actual text and figures** of the incorporated document do not constitute new matter See, e.g., M.P.E.P 2163.07 (b).

By Applicants own arguments, it is acknowledged that replacing subject matter incorporated into an application by reference with the **actual text and figures** of the incorporated document do not constitute new matter. Therefore incorporation of the actual text or figures from Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503 would be proper. However, neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the method steps of claims 7-73. Applicants may **point to the actual text** of the referred article of Harrington and Lieber (1995) or the issued patent in overcoming this rejection. There is no support in the instant specification or the incorporated reference that identifies the actual text which would indicate that the invention of claims 7-73 was conceived at the time of filing this application. Further there is no basis for methods of cleaving, detecting or formation of a hybridization complex or a kit - where the target nucleic acid having a first or second portion, or where 3'-probe comprises a 3'-flap region that is 1, 1-10 or 1-20 nucleotides in length (Claims 14-16, 31-33, 48-50, 56-58, 62-64). How is a single nucleotide cleaved ? It may also be noted that the incorporated reference shows cleaving of the DNA molecule (not RNA) therefor has no basis for 'polynucleotide' cleavage - RNA is not cleaved by

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FEN-1 (Harrington and Lieber, 1995, see page 1240, column 2, last 2 lines). Similarly there is no basis for 'polynucleotides' in the claims, whether it is for methods of cleavage or complexes or kits.

Claims 7-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 7-73 are directed to method steps using 'double-flap' structures, hybridization complexes and kits, which claims have no support in the specification of the issued patent or in the reference of Harrington and Lieber (1995). The method steps claimed had no basis or clearly outlined in the prior application or the issued patent. Claims also lack Flap endonuclease assay for measuring cleavage activity as well as hybridization conditions for use in complexes and kits.

Effective incorporation by reference is lacking. Applicants must clearly point out where in specification (or issued patent) or in the properly incorporated reference such methods or complexes have a clear-cut basis, or the invention was conceived at the time of filing this application.

Applicants cite numerous case laws, including *In re Voss*, 194 USPQ 267 (CCPA 1977) and *re Hughe*, 193 USPQ 141 (CCPA 1977). However, since the incorporation of the subject matter is improper, the referenced case laws do not apply.

9. ***Written Description***

Claims 7-10, 14-27, 31-44, 48-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method of cleaving a polynucleotide (claims 7-10, 14-27), a method of detecting the presence of target nucleic acid (claims 31-44), a hybridization complex (claims 48-58) and a kit for detecting the presence of a target nucleic acid (claims 59-70). The instant claims contain no limitations that define the structures of the claimed endonuclease (or FEN-1 SEQ ID NO :) or the strand that FEN-1 uses as substrate, used for cleaving a polynucleotide comprising the 3' and 5' regions or that used in the detection method or for hybridization complex and kit. FEN-1 cleavage is flap strand specific and independent of flap strand length [Harrington & Lieber, 1994, see abstract]. There is no description of the specific hybridization conditions used.

Applicants' argue that claims 7-73 are rejected for lack of written description. That is not the case. Only claims 7-10, 14-27, 31-44, 48-70 are rejected.

Applicants further argue that the original disclosure teaches diagnostic methods and probe polynucleotides capable of specific hybridization to the target and forming, as a result of such hybridization, a 5'-flap structure which can be cleaved by FEN-1.

In response, it is pointed out the claims (e.g. claims 7-9, 14-20) do not recite endonuclease FEN-1 and its structure (e.g. claims 7-10, 14-27, 31-44, 48-70) as argued. While the specification describes three species of FEN-1 polypeptides - human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3) and yeast FEN-1 (SEQ ID NO : 5) bearing close sequence homology or the

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isolation of endonuclease activity RAD2 : SEQ ID NO : 7, calf thymus, rabbit reticulocytes, etc., but which differ in other respects and is not representative of the entire 'FEN-1' genus.

10. Claims 7-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to claims 7-73, directed to a nucleic acid probe that specifically hybridizes to another or target nucleic acid(s), Applicants have not sufficiently defined the conditions under which the hybridizations are to take place. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed. The buffer composition, pH, temperature, length of time, salt concentrations, quality and source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the nature of hybridization experiments in general, it is not sufficient to merely cite hybridization without a clear and explicit recitation of the conditions associated with the hybridization. For example, the definition of stringency as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory. Therefore, without a clear and explicit recitation of the conditions which were actually used by Applicants in isolating the claimed polynucleotides which hybridize to the disclosed sequences, the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention. Without such guidance, the experimentation left to those skilled in the art is undue.

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Applicants arguments elude description to hybridization conditions. No specific hybridization conditions are described in the col. 39, line 65 through col. 40, line 18, as argued.

11. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: cleaving the 5' flap labeled structure by FEN-1, releasing the nucleotide in the flap strand; incubating with FEN-1 and detection the release of nucleotides (polynucleotide) of the flap strand and quantifying the released label as a measure of abundance of the target polynucleotide in the sample. The clarity of the steps is important.

Applicants argue that the amended claim 7 recite 'selectively cleaving' - which step subsumes (or encompass) the cleavage, release and incubation steps the Patent Office believes are omitted. While the disclosure at Col. 11, line 11 recites 'incubating with FEN-1' which when read in the context of the complete disclosure, skilled artisans would immediately recognize that this passage supports step (b) as presently drafted.

In response it is stated that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, an important method step cannot be assumed and such a step is not encompassed by the claim.

12. ***Rejection under 35 U.S.C. 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington and Lieber [EMBO JOURNAL, (1994 Mar 1) 13 (5) 1235-46, IDS]. Harrington et al. teach a DNA flap as a bifurcated structure composed of double-stranded DNA and a displaced single-strand. To identify DNA flap cleaving activities in mammalian nuclear extracts, the reference teaches an assay utilizing a synthetic DNA flap substrate. This assay has allowed the first purification of a mammalian DNA structure-specific nuclease. The enzyme described here, flap endonuclease-1 (FEN-1), cleaves DNA flap strands that terminate with a 5' single-stranded end. As expected for an enzyme which functions in double-strand break repair flap resolution, FEN-1 cleavage is flap strand-specific and independent of flap strand length. Furthermore, efficient flap cleavage requires the presence of the entire flap structure. Substrates missing one strand are not cleaved by FEN-1. In addition to endonuclease activity, FEN-1 has a 5'-3' exonuclease activity which is specific for double-stranded DNA. The endo- and exonuclease activities of FEN-1 are discussed in the context of DNA replication, recombination and repair. (see abstract, Figure 1, DNA substrate oligonucleotides, cleavage of flap structure derivatives, Figures 5-10 and discussion).

The teachings of the reference identifies a purified nuclease from mouse which is specific for DNA flap structures. The cleavage of the 5'-flaps by FEN-1 (flap endonuclease 1) was unrelated in

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sequence (see discussion, page 1243, column 1-2), was independent of flap strand length (varying nucleotide length, may be 1, 1-10 or 20) and always occurred in a strand specific fashion such that only 5' flap strand of the polynucleotide was cleaved, and monitored by detecting label contained in the 5'-end (see Fig. 5 and 7, for example.).

The reference does specifically teach the method steps as claimed, however uses an obvious variation of cleaving a polynucleotide using a FEN-1 and measuring the detectable radio-label, which are visualized by autoradiography.

It would have been obvious for one of ordinary skill in the art, to recite or make the obvious method steps variations or changes using the detailed methodology presented in the cited reference of Harrington et al. by cleaving the polynucleotide using the FEN-1 polypeptide or catalytically active fragments thereof or substitute the FEN-1 polypeptide with other known endonucleases (or that of specific SEQ ID nos.) and monitor the radio labeled product for the detection of target nucleic acid in a sample (claims 7-50), using the hybridization complexes (claims 51-58) as FEN-1 substrates (many of which are taught by the Harrington et al.) or develop a kit (claims 59-73) using the method outlined above for the detection of target nucleic acid. One of ordinary skill in the art would have been motivated to make or modify the method suitably, in view of the suggested importance of the roles of FEN-1 in DNA replication, DNA repair and recombination (see introduction), and do so with a reasonable expectation of success.

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Applicants argue that Harrington et al. do not teach double-flap structure and that all the independent claims 7, 21, 36..... recite 'double flap structure' and therefore all the limitations are not taught.

In response none of claims recite the phrase 'double flap'. The specification does not distinguish double flap from bifurcated structure taught by Harrington et al. Therefore, the rejection is maintained.

13. Claims 1-6 are allowed.

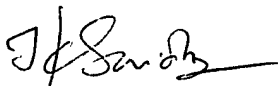
14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Tekchand Saidha

Primary Examiner, Art Unit 1652

July 9, 2002